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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/633,093	08/04/2000	Joel S. Greenberger	07787-004003	2079

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EXAMINER

LI, QIAN J

ART UNIT PAPER NUMBER

1632

DATE MAILED: 04/23/2002

7

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/633,093

Applicant(s)

GREENBERGER ET AL.

Examiner

Janice Li

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 February 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11 and 21-30 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-11 and 21-30 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: *detailed action*.

DETAILED ACTION

The amendment filed on February 1, 2002 has been entered and as assigned as Paper #6. Claim 1 has been amended. Claims 21-30 are newly added. Currently, claims 1-11 and 21-30 are pending and under examination

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The prior rejection of claims 1-11 under 35 U.S.C. 112, second paragraph, is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-5, and 7-10 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Anderson et al* (US 5 399 346, 3-21-1995), taken with *Greenberger et al* (EP 0 381 490 A2, 8-8-90), and *Boswell et al* (Exp. Hematol 1983), and the rejection applies to newly submitted claims 21, 22, 24-26, 29, and 30 for reasons of record and the following.

Art Unit: 1632

Applicants argue that *Anderson et al* discloses neither BMSCs nor the level of gene expression in cryopreserved and subsequently thawed T cells; that the *cells* of the present invention and those disclosed in the Anderson reference are significantly different, thus, the cryopreservation could have different effects on TILs relative to BMSCs.

In response, it is acknowledged that the claims are directed to a method of cryopreservation particularly for transduced BMSCs. It is noted that cryopreservation of cells in general is a well-known technique in the art, and widely used in the preservation of all cell types, including hematopoietic stem cells and marrow cells as taught by *Boswell et al*. Neither prior art of record nor the specification teaches that cryopreservation of one cell type would be different from the other, particularly considering both T cells and BMSCs are derived from bone marrow. Further, the specification fails to teach a different process that would be particularly suitable for BMSCs over other cell types. It is also noted that transduced BMSCs differ from untransduced BMSCs in that they are transformed with nucleic acids, which nucleic acids are generally resistant to freeze and thaw process, they are routinely preserved at low temperature condition. It is the common knowledge in the art that the design of cryopreservation technique is aimed at using penetrating cryoprotectant to protect cells from the injury associated with ice formation. The cryopreserving procedure used in the instant application is a standard procedure effective for both TILs and BMSCs. Therefore, the instant claimed invention is obvious over Anderson reference.

Concerning the levels of gene expression among cryopreserved TILs and BMSCs, applicants are reminded that the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the prior art products do not necessarily or inherently possess characteristics of claimed product, which requires factual evidence demonstrating that actual, unobvious differences exist, and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPBI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray* 10 USPQ2d 1922, 1923 (BPAI 1989).

Applicants further argue that *Greenberger et al* discloses the use of BMSCs for gene therapy, contains no information of cryopreservation, *Boswell et al* discloses cryopreservation of untransfected bone marrow cells, contains no information regarding TILs. Applicants are at a loss to understand the basis for combining the disclosures of the recited references.

In response, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In this case, it is known in the art that nucleic acid transduced

Art Unit: 1632

cells could be cryopreserved, that BMSCs could be well preserved by the standard cryopreserving technique, that BMSCs are favorably considered in carrying exogenous gene for gene therapy. Therefore, it would have been obvious to one of ordinary skill in the art to modify the method taught by *Anderson et al* by simply substituting T lymphocytes or other blood-borne primary cells with BMSCs as taught by *Greenberger et al* and *Boswell et al* in cryopreservation. The ordinary skilled artisan would have been motivated to modify the claimed invention in cryopreserving of transduced BMSCs or other transduced cell type to avoid repeated painful clinical procedure in obtaining BMSCs. The ordinary skilled artisan would have been sufficiently motivated to do so for any types of primary cells, at any stage of the experimentation, i.e. before or after DNA transfection, such as taught by *Anderson et al*. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-10 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Anderson et al* (US 5 399 346, 3-21-1995), *Greenberger et al* (EP 0 381 490 A2, 8-8-90), and *Boswell et al* (Exp. Hematol 1983), as applied to claims 1-5, 7-10 above, and further in view of *Lozier et al* (Hum Gene Ther 1994); and the rejection applies to newly submitted claims 21-26, 29, and 30 for the reasons of record and following.

Applicants argue that *Lozier et al* reference provide no basis to overcome the deficiencies of the combined teachings of *Anderson et al*, *Greenberger et al*, and *Boswell et al*, that *Lozier et al* taught a process comprising the steps of first cryopreserving the BMSCs, then thawing and transducing the cells.

In response, the Loister reference is applied for the teaching of a canine model. Although the more common practice in the art is demonstrated by *Loister et al*, i.e. transforming the BMSCs after thawing, this could be done in a different way as taught by *Anderson et al*, as long as the cells are viable, an exogenous gene could be expressed at a appropriate level meeting the claim limitation, regardless whether they are transformed before or after the cryopreservation. Again, the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the prior art products do not necessarily or inherently possess characteristics of claimed product, which requires factual evidence demonstrating that actual, unobvious differences exist, and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPBI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray* 10 USPQ2d 1922, 1923 (BPAI 1989). Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-5 and 7-11 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Anderson et al* (US 5 399 346, 3-21-1995), *Greenberger et al* (EP 0 381 490 A2, 8-8-90), and *Boswell et al* (Exp. Hematol 1983), as applied to claims 1-5 and 7-10 above, and further in view of *Lobb et al* (Biochem Biophy Res Com, 1991).

Applicants argue that *Lobb et al* publication provides no information regarding cyopreservation of transfected BMSCs, that they transduced CHO cells not lymphocytes.

In response, the *Lobb et al* reference is applied for the teaching of expressing cell surface molecules, such as V-CAM, for lymphocyte targeting. Again, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, the combined teachings suggest that a skilled artisan knows an adhesion molecule could be used for lymphocyte targeting, and the ordinary skilled artisan would have been motivated to modify the claimed invention using an adhesion molecule in targeting BMSCs with a reasonable expectation of success. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

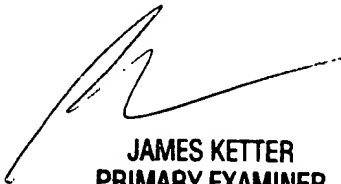
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Application/Control Number: 09/633,093
Art Unit: 1632

Page 9

Q. Janice Li
Examiner
Art Unit 1632

QJL
April 19, 2002



**JAMES KETTER
PRIMARY EXAMINER**